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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,307	08/07/2006	John C. Gebler	64254(49991)	1965

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EXAMINER	
XU, XIAOYUN	

ART UNIT	PAPER NUMBER
1797	

MAIL DATE	DELIVERY MODE
12/14/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,307	GEBLER ET AL.	
	Examiner	Art Unit	
	ROBERT XU	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *4-13,15-18,24,52,58-60,66,70-72,84-87,90,91 and 93* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 23, 37, 41, 44, 51, 56, 57, 65, 73, 77, 79, 83, 88, 99 and 100* is/are rejected.

7)☒ Claim(s) *23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,2,4-13,15-18,23,24,37,41,44,48-52,56-60,65,66,70-73,77,79,83-88,90,91,93,99 and 100.

DETAILED ACTION

1. The amendment filed on 11/11/2009 has been entered and fully considered. Claims 1-2, 4-13, 15-18, 23, 24, 37, 41, 44, 48-52, 56-60, 65, 66, 70-73, 77, 79, 83-88, 90, 91, 93, 99 and 100 are pending, of which Claims 4-13, 15-18, 24, 52, 58-60, 66, 70-72, 84-87, 90, 91 and 93 are presently withdrawn. Claims 3, 46 and 69 are canceled. Claims 1, 2, 23, 37, 41, 44, 51, 56, 57, 65, 73, 77, 79, 83, 88, 99 and 100 are considered on merits, of which, Claims 1, 37, 41 and 64 are amended, and Claim 99 and 100 is newly added.

Response to Amendment

2. In response to amendment, the examiner raises objection and modifies rejection over the prior art established in the previous Office action.

Claim Objections

3. Claim 23 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 23 depends on Claim 1. Claim 23 recites "substituted or unsubstituted aryl group" which broadened the limitation of the newly amended Claim 1.

Claim Rejections - 35 USC § 103

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. **Claims 1, 2, 23, 37, 41, 44, 51, 56, 57, 65, 73, 77, 79, 83, 88 and 99** are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang et al (Analytical Biochemistry, 1999, IDS) (Huang).

In regard to Claim 1, Huang teaches a method of preparing a sample for mass spectrometry analysis. The method comprises:

a) obtaining a sample comprising an analyte (peptide from tryptic digested protein), the analyte comprises an exposed group (NH_2-terminus) (see page 307, right col. 2nd paragraph); and

b) reacting the analyte (peptide) with a triarylphosphonium labeling reagent (Tris(trimethoxyphenyl)phosphonium (TMPP) reagents) having a reactive group (acetyl-O-succinimide (AcOSu)) capable of reacting with the exposed group (NH_2-terminus) to form a triarylphosphonium-linked analyte (see page 307, right col. 3rd paragraph).

wherein the labeling reagent has a structure according to the formula

$[Ar_3P^+R]X^-$,

wherein

each Ar is an aryl group (methoxyphenyl) (see Scheme 1);

P is a phosphorous atom (see Scheme 1);

R is a reactive group comprising a functional group (AcOSu) that react with the exposed group (NH2-terminus) to form a covalent bond thereby forming triarylphosphonium-linked analytes (TMPP-Ac-peptide) (see Scheme 1); and

X^- is a negatively-charged counter ion (Br^-) (see Scheme 1).

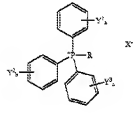
Huang does not teach that the Ar is unsubstituted. Huang teaches that the Ar is substituted. However, based on the structure of the labeling reagent, the substitution on the aryl group does not significantly affect the reactivity of the R group. The instant specification also admits that Ar group is selected from group consisting of substituted or unsubstituted aryl group (see page 18, lines 26-27). At time of the invention it would have been obvious to one of ordinary skill in the art to use unsubstituted aryl group in Huang's method, because the unsubstitution on the aryl group does not significantly affect the reactivity of the R group.

In regard to Claim 2, Huang teaches that the method comprising the further step of obtaining the triarylphosphonium labeling reagent having a reactive group (see page 307, left col. 3rd paragraph).

In regard to Claim 23, Huang teaches that the Ar group is substituted aryl group (methoxyphenyl) (see Scheme 1).

In regard to Claim 37, Huang does not teach that the Ar_3P is unsubstituted. Huang teaches that Ar_3P group is substituted triphenylphosphophine (trimethoxyphenylphosphine) (see Scheme 1). As has been discussed in regard to Claim 1, at time of the invention it would have been obvious to one of ordinary skill in the art to use unsubstituted aryl group in Huang's method, because the unsubstitution on the aryl group does not significantly affect the reactivity of the R group.

In regard to Claim 41, Huang teaches that the labeling reagent has a structure according to the formula



wherein

P is phosphorous atom (see scheme 1);

R is a reactive group (AcOSu) comprising a functional group that reacts with the exposed functional group (NH_2-terminus) to form a covalent bond thereby forming triarylphosphonium-linked analytes (see scheme 1);

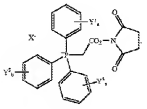
a, b, and c are 3 (see scheme 1);

Y^1, Y^2, and Y^3 are alkoxyl (see scheme 1);

X^- is a negatively-charged counter ion (Br^-) (see scheme 1).

Huang does not teach that the Ar is unsubstituted. Huang teaches that the Ar is substituted. As has been discussed in regard to Claim 1, at time of the invention it would have been obvious to one of ordinary skill in the art to use unsubstituted aryl group in Huang's method, because the unsubstitution on the aryl group does not significantly affect the reactivity of the R group.

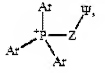
In regard to Claim 44, Huang teaches that the labeling reagent has a structure according to the formula (TMPP-Ac-O-Su) (see Reagent 2 in scheme 1).



In regard to Claim 51, Huang teaches that the exposed group of the analyte (N-terminal group of peptide) is electrophilic and the reactive functional group (O-succinimide (OSu)) is nucleophilic (see scheme 1).

In regard to Claim 56, Huang teaches that X^- is a halide (Br^-) (see scheme 1).

In regard to Claim 65, Huang teaches that the labeling reagent has the following structure:



wherein

each Ar is aryl group (methoxyphenyl) (see scheme 1);

P is a phosphorous atom (see scheme 1);

Z is a linking group (Ac) (see scheme 1); and

Ψ is a reactive functional group (OSu) (see scheme 1).

In regard to Claim 73, Huang teaches that Ψ group is an isocynate (OSu) (see scheme 1).

In regard to Claim 77, Huang teaches that Ψ group is an aryl halide (SC_6F_5) (see scheme 1).

In regard to Claim 79, Huang teaches that Z has 3 nonhydrogen atoms selected from group consisting of C, N, O and S, and the longest liner segment contains 2 nonhydrogen atoms (see scheme 1).

In regard to Claim 83, Huang teaches that the analyte is a peptide (see scheme 1, page 307).

In regard to Claims 88 and 99, Huang does not specifically teach that the sample is a biological tissue. It is well known that proteins can be obtained from biological tissue. At the time of the invention it would have been obvious to one of ordinary skill in the art to analyzing a biological tissue that contains proteins.

6. **Claims 1, 41, 50, 88, 99 and 100** are rejected under 35 U.S.C. 103(a) as being unpatentable over Leavens et al (Rapid Communications in Mass Spectrometry, 2002, IDS) (Leavens).

In regard to Claim 1, Leavens teaches a method of preparing a sample for mass spectrometry analysis. The method comprises:

a) obtaining a sample comprising an analyte (amines) (see Table 1), the analyte comprises an exposed group (amine group) (see page 439, right col. 1st paragraph); and

b) reacting the analyte (amines) with a triarylphosphonium labeling reagent (TMPP-reagents) having a reactive group (carboxylic group) capable of reacting with the exposed group (amine group) to form a triarylphosphonium-linked analyte (see Table 3, page 439, right col. 1st paragraph).

wherein the labeling reagent has a structure according to the formula

$[Ar_3P^+R]X^-$,

wherein

each Ar is an aryl group (methoxyphenyl) (see Scheme 1);

P is a phosphorous atom (see Scheme 1);

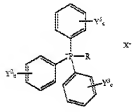
R is a reactive group comprising a functional group (carboxylic group) that react with the exposed group (NH2-terminus) to form a covalent bond thereby forming triarylphosphonium-linked analytes (TMPP-Ac-peptide) (see Scheme 1); and

X^- is a negatively-charged counter ion (Br^-) (see Scheme 1).

Leavens does not teach that the Ar is unsubstituted. Leavens teaches that the Ar is substituted. However, based on the structure of the labeling reagent, the substitution on the aryl group does not significantly affect the reactivity of the R group. The instant specification also admits that Ar group is selected from group consisting of substituted or unsubstituted aryl group (see page 18, lines 26-27). At time of the

invention it would have been obvious to one of ordinary skill in the art to use unsubstituted aryl group in Leavens' method, because the unsubstitution on the aryl group does not significantly affect the reactivity of the R group.

In regard to Claim 41, Leavens teaches that the labeling reagent has a structure according to the formula



wherein

P is phosphorous atom (see scheme 1);

R is a reactive group comprising a functional group (carboxylic group) that reacts with the exposed functional group (amine group) to form a covalent bond thereby forming triarylphosphonium-linked analytes (see Table 3);

a, b, and c are 3 (see scheme 1);

Y^1, Y^2, and Y^3 are alkoxyl (see scheme 1);

X^- is a negatively-charged counter ion (Br^-) (see scheme 1).

Leavens does not teach that the Ar is unsubstituted. Leavens teaches that the Ar is substituted. As has been discussed in regard to Claim 1, at time of the invention it would have been obvious to one of ordinary skill in the art to use unsubstituted aryl group in Leavens' method, because the unsubstitution on the aryl group does not significantly affect the reactivity of the R group.

In regard to Claim 50, Leavens teaches stable isotopically labeling of TMPP 'tag' with ^{13}C and ^{2}H for mass spectrometry analysis of target molecule (see abstract, page 441, left col. 1st paragraph).

In regard to Claims 88 and 99, Leavens teaches a method of preparing a sample for mass spectrometry analysis, comprising

a) obtaining a sample comprising an analyte (amines) having an exposed group (amine group) (see page 439, right col. 1st paragraph, Table 1); and

b) reacting the analyte (amines) with a triarylphosphonium labeling reagent (TMPP-reagents) having a reactive group (carboxylic group) capable of reacting with the exposed group (amine group) to form a triarylphosphonium-linked analyte (see Table 3, page 439, right col. 1st paragraph).

Leavens does not specifically teach that the sample is a biological tissue. It is well known that amines can be obtained from biological tissue. At the time of the invention it would have been obvious to one of ordinary skill in the art to analyzing a biological tissue that contains amines.

In regard to Claim 100, Leavens teaches that the analyte is a small molecule (amines) (see Table 1).

Response to Arguments

7. Applicant's arguments filed 11/11/2009 have been fully considered but they are not persuasive.

Applicant amended Claims 1, 41 and 65 to narrow the aryl group to unsubstituted aryl group. Based on the structure of the labeling reagent, the substitution on the aryl group does not significantly affect the reactivity of the R group. The instant specification and Claim 23 also admit that Ar group is selected from group consisting of substituted or unsubstituted aryl group (see page 18, lines 26-27). At time of the invention it would have been obvious to one of ordinary skill in the art to use unsubstituted aryl group in Huang's method, because the unsubstitution on the aryl group does not significantly affect the reactivity of the R group.

Applicant argues that Huang or Leavens does not teach analyzing biological tissue sample. Huang teaches analyzing peptide that has an exposed functional group that reacts with the reactive group of the labeling reagent. Leavens teaches analyzing amines and carboxylic acid compounds that react with the reactive group of the labeling reagent (see Table 1 & 2). Many biological samples contain peptides, amines or carboxylic acids. It would have been obvious for a routineer to analyze a biological tissue sample that contains peptides or amines or carboxylic acids or any molecules

that contains functional group that reacts with the reactive group of the labeling reagent as taught by Huang or Leavens.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT XU whose telephone number is (571)270-5560. The examiner can normally be reached on Mon-Thur 7:30am-5:00pm, Fri 7:30am-4:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Vickie Kim can be reached on (571)272-0579. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

12/8/2009

/Yelena G. Gakh/
Primary Examiner, Art Unit 1797

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